REMARKS

Claims 42, 45-49 and 53-61 are pending. As disclosed herein, Claim 42 is currently amended, and Claim 43 has been cancelled. Support for newly amended Claim 42 can be found in the instant Application at Claim 43, and paragraph [0055] of the published application. No new matter has been introduced. Applicants also thank the Examiner for the telephonic interview with Applicants' counsel on December 17, 2008 in which issues described herein were discussed. Applicants respectfully request reconsideration of the claims in light of the following arguments. The Application is in a condition for allowance.

Claim Rejections – 35 U.S.C. § 102

Claims 42, 45, 47-49, 54, 59 and 61 were rejected under 35 U.S.C. § 102(e) as anticipated by Young *et al.* (WO 03/018040) in light of Dua *et al.* (*Br. J. Ophthalmol.* 1999) or Tseng (U.S. 6,152,142; IDS ref. #1). The Examiner stated that Young *et al.* teach a method and a composite graft for the treatment of conditions associated with photoreceptor loss (*e.g.*, age-related macular degeneration), where the composite graft comprising RPE cells is grown on base membrane such as amniotic membrane. (10/28/08 Office Action at 6.) The Examiner also stated that Dua *et al.* teach that the amniotic membrane produces various growth factors and Young *et al.* teaches that amniotic membrane inherently comprises basement membrane and stroma. (*Id.* at 7.)

Applicants respectfully traverse Examiner's § 102 rejection for the following reasons. Newly amended Claim 42 claims a method for treating a retinal disease, comprising inserting in a subretinal space of a patient in need thereof a composite comprising amniotic membrane and non-immortalized retinal pigment epithelial cells or non-immortalized retinal pigment epithelial equivalent cells on the membrane, wherein the number of non-immortalized retinal pigment epithelial cells or non-immortalized retinal pigment epithelial equivalent cells on the membrane is from about 16,000 to about 20,000 per 4 mm^2 of amniotic membrane. Thus, Claim 42 as amended requires that the RPE or RPE equivalent cells on the membrane number between 16,000 to about 20,000 per 4 mm^2 of amniotic membrane.

Young *et al.* does not teach a composite comprising amniotic membrane and non-immortalized retinal pigment epithelial cells or non-immortalized retinal pigment epithelial equivalent cells on the membrane, wherein the number of non-immortalized retinal pigment

epithelial cells or non-immortalized retinal pigment epithelial equivalent cells on the membrane is from about 16,000 to about 20,000 per 4 mm^2 of amniotic membrane, nor do Dua *et al.* or Tseng *et al.* Therefore, Young *et al.* in light of Dua *et al.* or Tseng *et al.* does not anticipate the claimed subject matter, and the Examiner's § 102 rejection over Young *et al.* in light of Dua *et al.* or Tseng *et al.* should be withdrawn.

Claim Rejections – 35 U.S.C. § 103

Young et al.

Claims 42, 43, 45-49, 57-59 and 61 were rejected under 35 U.S.C § 103(a) as unpatentable over Young *et al.* (*supra*). The Examiner stated that although Young *et al.* is silent in the concentration of RPE cells being confluent or 16,000 to about 20,000 per 4 mm^2 of amniotic membrane, the concentration of RPE cells required for the graft taught by Young *et al.* would be considered as a result-effective variable that would be routinely optimized by one of ordinary skill in the art in practicing the invention. (10/28/08 Office Action at 8.)

Applicants respectfully traverse Examiner's § 103(a) rejection. Young *et al.* requires that "the RPE cells of the invention are delivered [onto a supporting membrane] as an intact epithelium." Young *et al.* at p. 13 (emphasis added). The present application provides the unexpected result that 16,000 to about 20,000 non-immortalized RPE or RPE equivalent cells per 4 mm^2 of amniotic membrane can be seeded and grown directly on the amniotic membrane, and do not need to be transferred onto the membrane as an epithelial monolayer sheet.

According to Young *et al.*, the intact epithelium monolayer is required for the RPE cells to form tight junctions with each other and exhibit a clearly defined polarity with distinct apical and basal surfaces. *Id.* at 14. Maintaining polarity is essential for important RPE cell functions such as active movement of fluid from vitreous to choroid to maintain retinal attachment, for catabolism of photoreceptor outer segment membranes, and for the blood-retinal barrier. *Id.* Young *et al.* further states that the integrity of the RPE as an epithelial monolayer sheet is important for keeping the RPE cells from migrating in destructive ways and resisting neovascular incursion, and that the RPE cells should be harvested as a sheet and that the layer should not be disturbed from its native apposition when delivered onto a supporting membrane. *Id.* In fact, Young *et al.* states that polarity is frequently lost when the RPE cells are not left in an intact sheet. *Id.*

Unlike Young *et al.*, the instant application does not require that the RPE cells be transferred onto the amniotic membrane as an intact epithelial sheet undisturbed from the native apposition. In the instant application, the non-immortalized RPE cells are harvested, and removed from their native sheet configuration. *See* Application at paragraph [0095]. The RPE cells are passaged and then seeded directly onto amniotic membrane, and are cultured and grown on the amniotic membrane. *Id.* at [0097], [0100]. The instant application provides the unexpected result that 16,000 to about 20,000 non-immortalized RPE or RPE equivalent cells per 4 mm^2 of amniotic membrane can be seeded and grown directly on the membrane, and do not have to remain in its native epithelial sheet configuration when transferred to the membrane. Unexpectedly, the particular composite comprising amniotic membrane and retinal pigment epithelial cells or retinal pigment epithelial equivalent cells on the membrane, wherein the number of retinal pigment epithelial cells or retinal pigment epithelial equivalent cells on the membrane is from about 16,000 to about 20,000 per 4 mm^2 of amniotic membrane allows the RPE cells to induce the proper epithelial phenotype, even though the RPE cells were disturbed from their native apposition and were not transferred to the amniotic membrane as an intact epithelial monolayer sheet. *See* Application at paragraphs [0100]-[0107].

Therefore, Young *et al.* actually teaches away from the present invention. Young *et al.* does not teach or suggest that about 16,000 to about 20,000 non-immortalized RPE or RPE equivalent cells per 4 mm^2 of amniotic membrane, disturbed from their native epithelial sheet and not delivered as an intact epithelium sheet onto the membrane, can be used successfully. Therefore, Examiner's § 103(a) rejection over Young *et al.* should be withdrawn.

Young et al. in view of Grueterich et al.

Claim 53 was rejected under 35 U.S.C § 103(a) as unpatentable over Young *et al.* in view of Grueterich *et al.* (2002; IDS ref. #28). Applicants traverse Examiner's § 103 rejection over Young *et al.* in view of Grueterich for the same reasons as above. Because the instant application provides for unexpected results over Young *et al.*, Examiner's § 103 rejection over Young *et al.* in view of Grueterich *et al.* should be withdrawn.

Young et al. in view of Tseng

Claims 54-58 were rejected under 35 U.S.C § 103(a) as unpatentable over Young *et al.* in view of Tseng. As before, Applicants traverse Examiner's § 103 rejection over Young *et al.* in view

of Tseng for the same reasons as above. Because the instant application provides for unexpected results over Young *et al.*, Examiner's § 103 rejection over Young *et al.* in view of Tseng should be withdrawn.

Liu in view of Dutt et al. in further view of Dua et al. and Young et al.

Claims 42, 43, 45-46, 49, 54, 57-59 and 61 were rejected over Liu (U.S. 6,045,791; IDS ref. #7) in view of Dutt *et al.* (1991; IDS ref. #15) in further view of Dua *et al.* and Young *et al.*

Applicants traverse Examiner's § 103 rejection for the following reasons. First, a skilled artisan would not have been motivated to replace the collagen substrate of Liu with the amniotic membrane of Dutt *et al.* because neither Liu or Dutt *et al.* anywhere teaches or suggests culturing non-immortalized RPE cells or non-immortalized RPE equivalent cells on an amniotic membrane, wherein the number of non-immortalized retinal pigment epithelial cells or non-immortalized retinal pigment epithelial equivalent cells on the membrane is from about 16,000 to about 20,000 per 4 mm^2 of amniotic membrane. Therefore, one of skill in the art would not combine Liu and Dutt *et al.* to achieve the claimed invention.

Dutt *et al.* describes an effort to grow human retinal pigment epithelium (HRPE) cell line 0041 – an immortalized cell line – on various matrices, including an amniotic membrane biomatrix. Dutt *et al.* notes that HRPE cell line 0041 is a cell line that has been characterized for growth. Dutt *et al.* at 1089. However, despite the use of a growth-characterized, immortalized HRPE cell line, Dutt *et al.* was unable to grow HRPE cell line 0041 on amniotic membrane biomatrix to a confluent concentration of from about 16,000 to about 20,000 per 4 mm^2 of amniotic membrane. Because Dutt *et al.* could not achieve this concentration of HRPE immortalized cells on amniotic membrane biomatrix, Dutt *et al.* would not suggest to one of ordinary skill in the art that primary, non-immortalized RPE cells, which "at best, undergo senescence and die after a few passages," would be **more** successful than immortalized RPE cells in reaching a confluent concentration from about 16,000 to about 20,000 per 4 mm^2 of amniotic membrane. *See id.* at 1089, 1096-97 (distinguishing non-immortalized primary RPE cells from immortalized RPE cells).

The present invention therefore provides the unexpected result that primary, non-immortalized RPE or RPE equivalent cells can be grown on amniotic membrane to a confluent concentration of from about 16,000 to about 20,000 per 4 mm^2 of amniotic membrane. In sum, one

of ordinary skill in the art would not combine Liu and Dutt *et al.* to obtain the present claimed invention.

Further, Dua *et al.* does not resolve the deficiencies of Liu in view of Dutt *et al.* Dua *et al.* discloses the use of amniotic membrane in the eye, but does not teach that amniotic membrane can be used for the same purpose as the collagen substrate of Liu for culturing non-immortalized RPE cells or non-immortalized RPE equivalent cells on an amniotic membrane, wherein the number of non-immortalized retinal pigment epithelial cells or non-immortalized retinal pigment epithelial equivalent cells on the membrane is from about 16,000 to about 20,000 per 4 mm^2 of amniotic membrane. Nor does Young *et al.* resolve the deficiencies of Liu in view of Dutt *et al.* The Examiner state that Young *et al.* teaches that the amniotic membrane is an equivalent for the Bruch's membrane. However, Young *et al.* does not teach or suggest culturing non-immortalized RPE cells or non-immortalized RPE equivalent cells on an amniotic membrane, wherein the number of non-immortalized retinal pigment epithelial cells or non-immortalized retinal pigment epithelial equivalent cells on the membrane is from about 16,000 to about 20,000 per 4 mm^2 of amniotic membrane. In sum, the Examiner's rejection using the 4-way combination of Liu (U.S. 6,045,791; IDS ref. #7) in view of Dutt *et al.* (1991; IDS ref. #15) in further view of Dua *et al.* and Young *et al.* should be withdrawn in its entirety.

Liu in view of Dutt in further view of Dua et al., Young et al., and Grueterich et al.

Claim 53 was rejected under 35 U.S.C § 103(a) using the 5-way combination of Liu in view of Dutt *et al.* in further view of Dua *et al.*, Young *et al.*, and Grueterich *et al.* Applicants respectfully traverse Examiner's rejection for the same reasons as stated above in Applicant's arguments that Claims 42, 43, 45-46, 49, 54, 57-59 and 61 are not obvious over Liu in view of Dutt *et al.* in further view of Dua *et al.* and Young *et al.* Therefore, the Examiner's rejection over Liu in view of Dutt *et al.* in further view of Dua *et al.*, Young *et al.*, and Grueterich *et al.* should be withdrawn in its entirety.

CONCLUSION

Applicant submits that this paper fully addresses the Final Office Action mailed October 28, 2008. Applicant respectfully solicits the Examiner to expedite prosecution of this patent application to allowance. Should the Examiner have any questions, the Examiner is encouraged to contact the undersigned attorney at (858) 350-2306. The Commissioner is authorized to charge any additional fees that may be required, including petition fees and extension of time fees, or credit any overpayment to Deposit Account No. 232415 (Docket No.: 34157-707.831).

Respectfully submitted,

WILSON SONSINI GOODRICH & ROSATI
A Professional Corporation

Date: December 29, 2008 By: _____

Michael J. Hostetler, Ph.D.
Reg. No. 47,664

650 Page Mill Road
Palo Alto, CA 94304
Direct Dial: (858) 350-2306
Customer No. 021971